Exhibit - A

Stability and compatibility of tegaserod from crushed tablets mixed in beverages and foods

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Purpose. The stability and compatibility of tegaserod from crushed tablets in selected beverages and foods were studied.

Methods. Suspensions of tegaserod maleate tablets containing 6 mg of the drug base were prepared by crushing the tablets and mixing the powder with tap water, apple juice, orange juice, milk, applesauce, yogurt, and chocolate–hazelnut spread. Drug stability, drug comparability, suspension homogeneity, and completeness of a dose were measured by high-performance liquid chromatography at intervals up to three days at 20–25 °C and 5 °C. In vitro dissolution profiles were determined for crushed tegaserod tablets in water, apple juice, orange juice, and applesauce.

Results. Tegaserod from crushed tablets was stable in and compatible with water, apple juice, orange juice, and applesauce, and the suspensions were homogeneous. The complete dose was delivered with these media. The dissolution profiles of crushed tegaserod tablets in water and in apple juice were comparable to those of intact tablets; the dissolution profiles in orange juice and applesauce were not comparable with those of intact tablets. The results with milk, yogurt, and chocolate–hazelnut spread as vehicles were inconclusive. The suspension in milk was not homogeneous, and the dose was incomplete.

Conclusion. Tegaserod from crushed tablets was stable in and compatible with water, apple juice, orange juice, and applesauce, but the dissolution profile in orange juice or applesauce was not acceptable. Apple juice may be the preferred vehicle because it masks the drug's taste.

Index terms: Beverages; Dissolution; Food; Gastrointestinal drugs; Homogeneity; Incompatibilities; Juices; Milk; Stability; Storage; Suspensions; Tegaserod maleate; Temperature

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Irritable-bowel syndrome (IBS) affects up to 20% of the North American population, particularly women.[1-6] Tegaserod maleate (Zelnorm, Novartis Pharmaceuticals, East Hanover, NJ) is a highly selective partial agonist of serotonin type 4 receptors that is indicated for use in the treatment of women with IBS with constipation (IBS-C). Unlike traditional medications (e.g., laxatives), which target only certain IBS symptoms, tegaserod provides global relief of the symptoms of IBS-C.[7-9] The pharmacokinetics of tegaserod are well defined, and the recommended dosage is 6 mg taken twice daily orally before meals for four to six weeks; continued use after six weeks is determined at the discretion of the physician.[9,10] Tegaserod is available as a white, uncoated tablet with a beveled edge.

Although an oral formulation has distinct advantages (e.g., many patients prefer pills or tablets to other routes of administration),[11,12] not all patients can swallow pills or tablets.[13-17] In particular, many elderly patients, patients with gastroesophageal reflux disease, and patients who have had a medication-related adverse event may be unable to swallow a tablet.[13-15] For such patients, an alternative method of tegaserod administration is highly desirable.

The purpose of this study was to determine the stability and compatibility of tegaserod from crushed tablets in selected beverages and foods. In addition, the homogeneity and in vitro dissolution profile of crushed tegaserod tablets were examined in each beverage or food to determine whether these vehicles allow for complete administration of a dose. The ability of these beverages and foods to mask the taste of tegaserod was also evaluated.

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Methods

Suspension preparation. Preparation of suspensions of tegaserod began with thorough crushing of tegaserod maleate tablets containing 6 mg of the drug base[a] in an aluminum foil pouch with the back of a metal teaspoon. The number of tablets crushed and the volume of vehicle used varied by experiment. The media tested included tap water, apple juice,[b] orange juice,[c] milk,[d] applesauce,[e] yogurt,[f] and a chocolate–hazelnut spread.[g] For stability testing, the powder that resulted from crushing one 6-mg tegaserod tablet was added to 50 mL of beverage (resulting in a liquid suspension of tegaserod 0.12 mg/mL) or to 1 tablespoon of food. For degradation product testing, the powder that resulted from crushing five 6-mg tegaserod tablets was added to 25 mL of beverage (resulting in liquid suspension of tegaserod 1.2 mg/mL) or to 1 tablespoon of food. For tests for completeness of a dose and suspension homogeneity, the powder produced by crushing one 6-mg tegaserod tablet was added to 50 mL of beverage in a glass or to 125 g of yogurt, 130 g of applesauce, or 1 tablespoon of chocolate–hazelnut spread. For in vitro dissolution tests, the powder from one crushed 6-mg tegaserod tablet was added to 50 mL of beverage or 1 tablespoon of food (applesauce only). Vehicles without tegaserod were used as controls.

The following numbers of identical suspensions were prepared for each experiment: one sample of each food vehicle for homogeneity testing; two samples of each beverage vehicle for stability, degradation product, and homogeneity testing; and six samples of each vehicle for dissolution testing. All samples were prepared at room temperature (20–25 °C) before being stored at tested temperatures for tested lengths of time.

Sample preparation for high-performance liquid chromatography (HPLC). *Stability tests.* Each 50-mL tegaserod suspension (one ZB MED tablet in water, apple juice, orange juice, or milk) was shaken vigorously by hand for 5–10 times in a 100-mL amber glass volumetric flask. Each preparation of one crushed tegaserod tablet in food (1 tablespoon of applesauce, yogurt, or chocolate–hazelnut spread) was mixed with a spatula in a 250-mL amber glass container until completely homogenized (by visual inspection). The tegaserod suspensions and mixtures were allowed to stand at the specified storage temperatures for the specified storage times. Immediately before assay, each tegaserod–beverage sample was rehomogenized by manual shaking (5–10 times) at 20–25 °C, and the flask was filled to the 100-mL mark with methanol.[h] For extraction, 100 mL of methanol was added to the tegaserod–food mixtures. Each sample (tegaserod–beverage or tegaserod–food) was then mixed at 20–25 °C for 30 minutes on a magnetic stir plate[i] at approximately 850 rpm, 10 minutes in a sonicator,[j] and 30 minutes on a magnetic stir plate at approximately 850 rpm. A portion of the methanol solution was centrifuged at 2500 rpm at 20–25 °C for 15 minutes, and 20 µL of the resulting clear solution was injected into the HPLC system.[k] Each sample was assayed in duplicate.

Degradation product determination. Each 25-mL tegaserod suspension (five crushed tegaserod tablets in water, apple juice, orange juice, or milk) was shaken vigorously by hand 5–10 times in a 50-mL amber glass volumetric flask. Each preparation of five crushed tegaserod tablets in food (1 tablespoon of applesauce, yogurt, or chocolate–hazelnut spread) was mixed with a spatula in an amber glass centrifugation tube until it was completely homogenized (by visual inspection). The tegaserod suspensions and mixtures were allowed to stand at the specified storage temperatures for the specified storage times. Immediately before assay, each tegaserod–beverage sample was rehomogenized by manual shaking (5–10 times) at 20–25 °C, and the flask was filled to the 50-mL mark with acetonitrile.[l] For extraction, 50 mL of water–acetonitrile (50:50 by volume) was added to the tegaserod–food mixtures. Each sample (tegaserod–beverage or tegaserod–food) was then mixed at 20–25 °C for 30 minutes on a magnetic stir plate at approximately 850 rpm, 10 minutes in a sonicator, and 30 minutes on a magnetic stir plate at approximately 850 rpm. A portion of the extraction solution was centrifuged at 2500 rpm at 20–25 °C for 15 minutes, and 25 µL of the resulting clear solution was injected into the HPLC system. Each sample was assayed in duplicate. For the alternative HPLC method for the determination of degradation products, 10 µL was injected and tested in duplicate.

Test for completeness of a dose. Each 50-mL tegaserod suspension (one crushed tegaserod tablet in water, apple juice, orange juice, or milk) was homogenized by stirring with a metal teaspoon and was transferred to a 100-mL amber glass volumetric flask (to simulate the patient drinking the contents of the glass, the empty glass was not rinsed); the volumetric flask was then filled to the 100-mL mark with methanol for extraction and testing. Extraction was performed as described for the stability tests. This test was performed in duplicate.

Test for suspension homogeneity. Each 50-mL tegaserod suspension (one crushed tegaserod tablet in water, apple juice, orange juice, or milk) was homogenized by stirring with a metal teaspoon. Fifteen milliliters (30% of the total volume of the mixed suspension) was withdrawn from the glass immediately after stirring and transferred to a 100-mL amber glass volumetric flask, which was immediately filled to the 100-mL mark with methanol. This test was done in duplicate. Each tegaserod–food preparation was mixed with a

nized (by visual inspection). Approximately one third of the mixture was withdrawn with a teaspoon or spatula and transferred to an amber glass bottle, and 100 mL of methanol was added. This process was repeated three times for analysis of the entire mixture. Each sample was then mixed at 20–25 °C for 30 minutes on a magnetic stir plate at approximately 850 rpm, 10 minutes in a sonicator, and 30 minutes on a magnetic stir plate at approximately 850 rpm. A portion of the methanol solution was centrifuged at 2500 rpm at 20–25 °C for 15 minutes, and 20 µL of the resulting clear solution was injected into the HPLC system. Each sample was analyzed in duplicate.

In vitro dissolution test. Each 50-mL tegaserod suspension (one crushed tegaserod tablet in water, apple juice, or orange juice) was added to 450 mL of dissolution medium (purified water[m]). Each 1-tablespoon preparation of tegaserod in applesauce was added to 500 mL of dissolution medium and the temperature maintained at 37 °C (±0.5 °C). After the transfer, the spoon and the spatula were rinsed in dissolution medium in the vessel to ensure complete transfer. In vitro dissolution was tested with USP Dissolution Apparatus 2, and the paddle[n] was rotated at 50 rpm. All tests were performed on six samples, each prepared from one tegaserod tablet and mixed as described previously. Dissolution of crushed tablets without any beverage or food vehicle was performed by adding the powder directly to 500 mL of dissolution medium (three samples) and by adding the dissolution medium to the powder (three samples). No significant difference was observed, so mean results for six samples are reported. Five milliliters of each sample was withdrawn from the dissolution vessel after 5, 15, 30, and 60 minutes of rotation. Each portion was centrifuged at 2500 rpm at 20–25 °C for 10 minutes and diluted. Each diluted sample was injected into the HPLC system.

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HPLC procedures. For HPLC measurement of tegaserod and degradation products, the initial time point (time zero) was considered to be approximately one minute after sample preparation. For each determination, two samples of each vehicle tested (beverage or food) were examined three days after storage at 5 °C (±3 °C), which is the recommended storage temperature for all the selected beverages and foods except the chocolate–hazelnut spread (20–25 °C). Two samples stored at 20–25 °C were also tested at the three-day time point for additional information on the stability of tegaserod in these substances. If the results warranted further investigation, two samples each were tested at additional time points and temperatures. Specifically, beverages were tested at 1 hour (storage at 20–25 °C) and 24 hours (storage at 5 °C and 20–25 °C) after preparation, and foods were tested at 24 hours (storage at 20–25 °C) after preparation.

Assay validation. For stability and homogeneity tests, the instrumentation included a constant-flow solvent-delivery system,[o] a C_8 column[p] maintained at 30 °C with a column heater,[o] a variable-volume injector,[o] an ultraviolet light detector[q] set at 220 nm, and an analogue-to-digital converter[r] linked to a chromatography data acquisition system.[s] The mobile phase consisted of acetonitrile and aqueous 0.05 M ammonium carbamate (55:45 by volume) delivered at a flow rate of 2 mL/min.

For determination of degradation products (water, apple juice, and applesauce), a slight modification of the HPLC method developed by Novartis Pharmaceuticals for the purity of tegaserod tablets was used. The instrumentation included a constant-flow solvent-delivery system, a C_8 column maintained at 30 °C with a column heater, a variable-volume injector, an ultraviolet light detector set at 220 nm, and an analogue-to-digital converter linked to a chromatography data acquisition system. The mobile phases consisted of acetonitrile:aqueous 0.05 M ammonium carbamate:triethylamine adjusted to pH 8 with concentrated phosphoric acid (200:800:0.5 by volume) (mobile phase A) and acetonitrile:aqueous 0.05 M ammonium carbamate:triethylamine adjusted to pH 8 with concentrated phosphoric acid (700:300:0.5 by volume) (mobile phase B), delivered at a flow rate of 1.5 mL/min on a linear gradient: time zero, A = 90%, B = 10%; time 20 minutes, A = 5%, B = 95%; time 24 minutes, A = 0%, B = 100%; time 34 minutes, A = 0%, B = 100%; and time 36 minutes, A = 90%, B = 10%.

For some of the beverages and foods tested (orange juice, milk, yogurt, and chocolate–hazelnut spread), these HPLC conditions did not allow for the selective separation of components of the matrix from potential degradation products of tegaserod. Therefore, the samples were analyzed with an alternative HPLC method. The instrumentation included a constant-flow solvent-delivery system, a C_{18} column[t] maintained at 40 °C with a column heater, a variable-volume injector, an ultraviolet light detector set at 220 nm, and an analogue-to-digital converter linked to a chromatography data acquisition system. The mobile phases consisted of water:acetonitrile: trifluoroacetic acid (900:100:1 by volume) (mobile phase A) and water: acetonitrile:trifluoroacetic acid (100: 900:1 by volume) (mobile phase B) delivered at a flow rate of 1 mL/min on a linear gradient: time zero, A = 80%, B = 20%; time 12 minutes, A = 10%, B = 90%; time 15 minutes, A = 10%, B = 90%; time 16 minutes, A = 80%, B = 20%; and time 22 minutes, A = 80%, B = 20%.

In vitro dissolution tests were performed according to the method developed by Novartis Pharmaceuticals for tegaserod tablets. The HPLC method used in assay determination was modified by using mobile phase consisting of acetonitrile:aqueous 0.2 M diammonium hydrogen phosphate adjusted to pH 4.6 with phosphoric acid (40:60 by volume) delivered at a flow rate of 2 mL/min.

One control suspension (vehicle without a crushed tegaserod tablet) was prepared for each beverage or food and was analyzed as the sample. Resulting chromatograms were compared for interference by any peak.

For assay and homogeneity testing, a 400-µg/mL (expressed in terms of tegaserod drug base) stock solution of tegaserod hydrogen maleate reference substance[a] was prepared in methanol on each day of HPLC. The standard solution of tegaserod was prepared by diluting the stock solution with methanol to a concentration of 60 µg/mL. The standard solution was injected in duplicate after approximately every fourth sample as a one-point external standard.

For degradation product testing, a 300-µg/mL (expressed in terms of tegaserod base) stock solution of the same reference substance was prepared in acetonitrile:water (50:50 by volume) on each day of HPLC. The standard solution of tegaserod was prepared by diluting the stock solution with acetonitrile:water (50:50 by volume) to a concentration of 12 µg/mL. The standard solution was injected in duplicate after approximately every fourth sample as a one-point external standard.

For in vitro dissolution testing, a 120-µg/mL (expressed in terms of tegaserod drug base) stock solution of the same reference substance was prepared in acetonitrile:water (50:50 by volume) on each day of HPLC analysis. The standard solution of tegaserod was prepared by diluting the stock solution with acetonitrile:water (50:50 by vol-

ume) to a concentration of 6 µg/mL solution was injected in duplicate after approximately every third sample as a one-point external standard.

Acceptance criteria. Tegaserod was considered to be stable in a vehicle if certain acceptance criteria were met for the time points examined. The values of acceptance for stability were 90–110% of the theoretical concentration at time zero and not more than 3% less than the initial concentration after storage. The value of acceptance was ≤0.5% for degradation product 515-91 and ≤0.2% each for other, unknown degradation products, for a total of not more than 1% for all unknown degradation products. Values of acceptance for the completeness-of-dose study for the entire sample were 90–110% of the theoretical content.

Results

In water. Tegaserod from crushed tablets was stable in tap water for up to three days at either 20–25 °C or 5 °C (Table 1). The completeness-of-dose study indicated that patients who take crushed tegaserod tablets in water receive the complete dose of the medication; mean recovery was 95.4% (Table 2). The suspension resulting from mixing a crushed tegaserod tablet with water was homogeneous.

The results of the dissolution study are summarized in Table 3 and Figure 1. No substantial difference was observed between the dissolution profile of a crushed tegaserod tablet in water and that of the intact tablet. The higher percentage of dissolution observed at 5 minutes for the crushed tablet (91.4% of theoretical content dissolved) compared with the intact tablet (54.2%) reflects disintegration of the tablet resulting from the crushing performed before dissolution. By 15 minutes, the dissolution of the intact tablet (92.3%) and of the crushed tablet (94.6%) was comparable; complete dissolution (>85%) was observed for both.

Although the suspension was easy to prepare, water did not mask the taste of tegaserod.

In apple juice. Tegaserod from crushed tablets was stable in apple juice for up to one hour at 20–25 °C and for up to three days at 5 °C (Table 1). The degradation observed for longer storage times was primarily due to hydrolysis and to the formation of degradation product 515-91.

The completeness-of-dose study indicated that patients who take a crushed tegaserod tablet in apple juice receive the complete dose of the medication; mean recovery was 92.6% (Table 2). The suspension resulting from mixing a crushed tegaserod tablet with apple juice was homogeneous.

No substantial difference was observed between the dissolution profile of an intact tegaserod tablet and that of a crushed tablet in apple juice (Table 3). At 15 minutes, dissolution was comparable (92.3% for intact tablets and 92.7% for crushed tablets in apple juice). Dissolution in apple juice was complete by 5 minutes, even though the medium's pH was lowered by the apple juice (from a range of 6.2–7.8 to a final pH of 3.7) and was therefore less favorable to the drug's stability. The suspension was easy to prepare, and apple juice effectively masked the taste of tegaserod.

In orange juice. Tegaserod from crushed tablets was stable in orange juice for up to 24 hours at 20–25 °C and for up to three days at 5 °C (Table 1). The degradation observed for longer storage times resulted mainly from hydrolysis and the formation of degradation product 515-91.

The completeness-of-dose study indicated that patients who take crushed tegaserod tablets in orange juice receive the complete dose; mean recovery was 92.8% (Table 2). The suspension resulting from mixing a crushed tegaserod tablet with orange juice was homogeneous.

The dissolution profile of a crushed tablet mixed with orange

Table 1.
Stability of Tegaserod after Mixing of Crushed Tablets with Beverages and Storage at 20–25 or 5 °C

Storage Condition	Mean % Initial Concentration Remaining[a]							
	Water				Apple Juice			
	Tegaserod	515-91[b]	Unknown, Individual[c]	Unknown, Total[d]	Tegaserod	515-91	Unknown, Individual	Unknown, Total
Time 0	98.9	<0.05	0.05	0.05	98.4	0.09	<0.05	<0.05
1 hr at 20–25 °C	NA[e]	NA	NA	NA	98.2	0.13	<0.05	<0.05
24 hr at 20–25 °C	99.6	<0.05	0.05	<0.05	94.4[f]	0.65[f]	0.14	0.20
24 hr at 5 °C	NA	NA	NA	NA	97.7	0.14	0.05	0.05
3 days at 20–25 °C	100.1	<0.05	0.07	0.13	87.0[f]	1.63[f]	0.28[g]	0.39
3 days at 5 °C	99.1	<0.05	0.06	0.09	96.7	0.33	0.06	0.12

Storage Condition	Mean % Initial Concentration Remaining							
	Orange Juice				Milk			
	Tegaserod	515-91	Unknown, Individual	Unknown, Total	Tegaserod	515-91	Unknown, Individual	Unknown, Total
Time 0	95.7	0.11	<0.1	<0.1	91.9	<0.05	...[g]	...
1 hr at 20–25 °C	NA	0.13	0.11	0.11	NA	NA	NA	NA
24 hr at 20–25 °C	94.8	0.41	<0.1	<0.1	93.0	<0.05	...	...
24 hr at 5 °C	NA	0.14	<0.1	<0.1	NA	NA	NA	NA
3 days at 20–25 °C	92.5[f]	0.91[f]	0.20	0.70	92.9	NA	NA	NA
3 days at 5 °C	95.4	0.23	0.18	0.67	93.7	NA	NA	NA

[a]Calculated on the basis of theoretical tegaserod content in one tablet ($n = 2$).
[b]Primary degradation product.
[c]Most abundant individual unknown degradation product.
[d]All unkown degradation products.
[e]NA = not available (not tested).
[f]Does not meet acceptance criteria.
[g]Insufficient resolution and selectivity of the chromatographic method did not allow calculation.

Table 2.
Completeness of Tegaserod Dose and Homogeneity of Suspension after Mixing with Beverages

Beverage	Mean Recovery (%)
Completeness of Dose	
Water	95.4
Apple Juice	92.6
Orange Juice	92.8
Milk	71.5[a]
Homogeneity of Suspension	
Water	100.7
Apple Juice	85.0
Orange Juice	87.0
Milk	59.1[a]

[a]Does not meet acceptance criteria.

juice was not comparable to that of an intact tablet (Table 3). Even after one hour, the mean percentage of the theoretical content of tegaserod from a crushed tablet dissolved was only 57.8%. The limited dissolution in orange juice may be attributable to changes in pH and solubility, the adsorption of the tegaserod powder to constituents of the medium, or some combination of these factors. These results obtained in vitro raise questions about the bioavailability of tegaserod in vivo if the tablet is administered with orange juice. Orange juice masked the taste of tegaserod, and the suspension was easy to prepare.

In milk. Tegaserod was relatively stable in milk; the content of tegaserod remained unchanged for up to three days at 20–25 °C or 5 °C (Table 1). However, poor resolution and selectivity of the resultant chromatograms under both sets of HPLC conditions tested did not allow for a definitive conclusion regarding the presence of potential degradation products; only product 515-91 was quantifiable, and then only at 24 hours at 20–25 °C.

Mixing a crushed tegaserod tablet with milk did not result in the recovery of a complete dose (Table 2). Only approximately 70% of the dose was recovered; hence, a patient would receive less than three fourths of the dose if milk was used as the vehicle. In addition, the whole tegaserod tablet was not homogeneously distributed in the milk–tegaserod suspension. An in vitro dissolution profile was not obtained for crushed tegaserod tablets in milk.

Although it was easy to prepare, the mixture of a crushed tegaserod tablet and milk was heterogeneous, and the resultant dose was incomplete. Whether milk masked the taste of tegaserod was not tested.

In applesauce. Tegaserod from crushed tablets was adequately homogeneous and stable in applesauce for up to 24 hours at 20–25 °C and up to three days at 5 °C (Tables 4 and 5).

The dissolution profile of a crushed tablet mixed in applesauce was not comparable to that of an intact tablet (Table 3). Even after one hour, the mean percentage of the theoretical content of tegaserod from a crushed tablet dissolved was only 79.3%. The limited dissolution in applesauce may be attributable to changes in pH and solubility, the ad-

Table 3.
Dissolution of Tegaserod Tablets

Time (min)	Mean ± S.D. % Theoretical Content Dissolved ($n = 6$)				
	Intact Tablets in Water	Crushed Tablets in Water[a]	Crushed Tablets in Apple Juice	Crushed Tablets in Orange Juice	Crushed Tablets in Applesauce
5	54.2 ± 7.7	91.4 ± 1.3	90.1 ± 1.3	55.3 ± 0.6[b]	79.8 ± 3.0[b]
15	92.3 ± 0.9	94.6 ± 1.5	92.7 ± 1.2	57.4 ± 0.7[b]	80.5 ± 1.4[b]
30	96.0 ± 2.0	96.9 ± 0.7	91.8 ± 0.6	57.7 ± 1.3[b]	78.5 ± 1.6[b]
60	98.0 ± 2.1	97.4 ± 0.9	91.1 ± 1.5	57.8 ± 0.8[b]	79.3 ± 2.0[b]

[a]Unlike preparation of beverage-vehicle samples, in which a crushed tegaserod tablet was suspended in 50 mL of beverage before being added to 450 mL of dissolution medium (water), crushed tegaserod was added directly to 500 mL of water ($n = 3$) or 500 mL of water was added directly to crushed tegaserod tablets ($n = 3$).
[b]Dissolution profile not comparable to that of intact tablet.

Figure 1. Dissolution profile of tablets of tegaserod 6 mg. The dissolution medium was purified water.

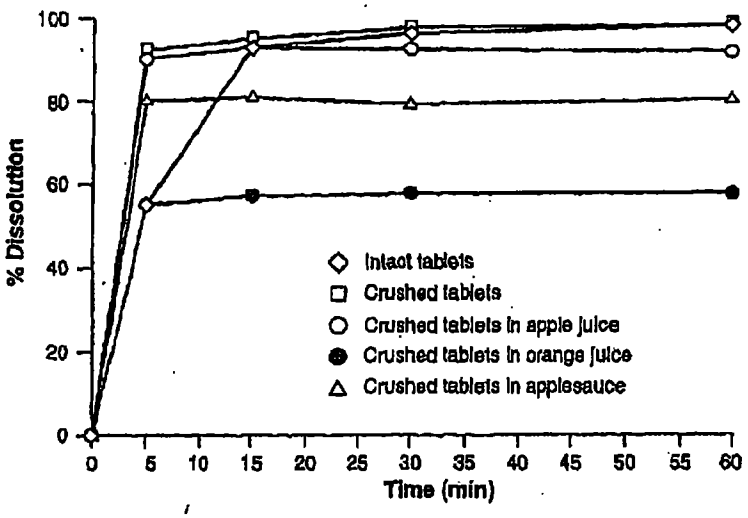

Table 4.
Homogeneity of Tegaserod Suspension after Mixing of Crushed Tablets with Foods

Food	% Recovery[a]	
	Individual Portions	Mean ± S.D.
Applesauce	70.9, 69.8, 68.0	69.6 ± 1.5
Yogurt	70.2, 68.4, 68.5	69.0 ± 1.0

[a]Compared with theoretical amount in a one-third fraction.

sorption of the tegaserod powder to constituents of the medium, or some combination of these factors. These results obtained in vitro raise questions about the bioavailability of tegaserod in vivo if the tablet is administered with applesauce. The mixture was easy to prepare, and applesauce effectively masked the taste of tegaserod.

In yogurt. The content of tegaserod in the mixture with yogurt appeared to remain unchanged (within the 3% limit allowed) for up to three days at 20–25 °C or 5 °C, indicating that tegaserod is stable in yogurt (Table 5). However, poor resolution and selectivity did not allow for a definitive conclusion about the presence of potential degradation products. Only degradation product 515-91 was quantifiable and only after 24 hours at 20–25 °C. A dissolution profile was not obtained for crushed tegaserod tablets in yogurt. More work is needed before a definitive conclusion can be reached on the stability of tegaserod in yogurt.

The mixture was easy to prepare and was adequately homogeneous (Table 4). Whether yogurt masked the taste of tegaserod was not tested.

In chocolate–hazelnut spread. Tegaserod in the mixture with chocolate–hazelnut spread remained stable for up to three days at 20–25 °C and 5 °C (Table 5). Poor resolution and selectivity did not allow for a definitive conclusion regarding the presence of potential degradation products, including 515-91. Although chocolate–hazelnut spread effectively masked the taste of tegaserod, its viscosity made sample preparation difficult. Consequently, no additional research was performed with this mixture.

Discussion

This study demonstrates that tegaserod can be administered in crushed tablet form in various media. Apple juice appears to be the best vehicle for crushed tegaserod tablets. The drug was stable in apple juice for up to one hour at 20–25 °C and up to three days at 5 °C. The in vitro dissolution profile of crushed tegaserod tablets in apple juice was comparable to that of intact tablets, indicating complete dissolution of tegaserod.

Table 5.
Stability of Tegaserod after Mixing of Crushed Tablets with Foods and Storage at 20–25 °C or 5 °C

Storage Condition	Mean % Initial Concentration Remaining[a]								
	Applesauce			Yogurt			Chocolate–Hazelnut Spread		
	Tegaserod	515-91[b]	Unknown, Individual[c]	Tegaserod	515-91	Unknown, Individual	Tegaserod	515-91	Unknown, Individual
Time 0	93.0	0.07	0.05	95.0	<0.05	...[d]	91.0	...	...
24 hr at 20–25 °C	93.5	0.22	0.12	94.5	0.13	...	92.1	...	...
3 days at 20–25 °C	93.9	0.56[e]	0.12	93.8	NA[f]	NA	89.8	...	...
3 days at 5 °C	95.2	0.13	0.12	95.6	NA	NA	89.9	...	...

[a]Calculated on the basis of theoretical tegaserod content in one tablet ($n = 2$).
[b]Primary degradation product.
[c]The most abundant unknown degradation product.
[d]Insufficient resolution and selectivity of HPLC did not allow calculation.
[e]Does not meet acceptance criteria.
[f]NA = not available.

ZB MEDension was easy to prepare and homogeneous, and the taste of tegaserod was effectively masked.

Tap water can also be used as a vehicle. Tegaserod was stable in this medium for up to three days at 20–25 °C or 5 °C, and the dissolution profile of a crushed tablet in water was the same as that of the intact tablet. However, water did not mask the taste.

Although tegaserod was stable in orange juice and in applesauce (for up to 24 hours at 20–25 °C and for up to three days at 5 °C) and both vehicles masked the taste and allowed the complete dose to be taken, neither is recommended for the administration of crushed tablets. The dissolution profiles of crushed tegaserod tablets in these media were not comparable to those of intact tablets, indicating incomplete dissolution of tegaserod and raising questions about bioavailability.

Inconclusive results on the stability of tegaserod in milk, yogurt, and chocolate–hazelnut spread leave unanswered the question of their suitability as vehicles for the administration of crushed tegaserod tablets; additional investigation is needed to optimize the extraction method and the HPLC separation of potential degradation products from the matrix. The mixture with milk was heterogeneous and resulted in an incomplete dose, and the viscosity of the chocolate–hazelnut spread made sample preparation difficult. None of these vehicles are recommended.

Conclusion

Tegaserod from crushed tablets was stable in and compatible with water, apple juice, orange juice, and applesauce. The dissolution profile of a crushed tablet mixed with orange juice or applesauce was not comparable to that of an intact tablet. Apple juice may be the preferred vehicle because it effectively masks the taste of tegaserod. Orange juice, milk, applesauce, yogurt, and chocolate–hazelnut spread are not recommended as vehicles for crushed tegaserod tablets.

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[a]Zelnorm, Novartis Pharmaceuticals Corporation, East Hanover, NJ, lot F006 0398.
[b]Auchan store brand, Croix, France, lot L11.
[c]Tropicana Pure Premium, Tropicana France, Villepinte, France, lot L297.
[d]Half-skim milk, Auchan store brand, Croix, lot 21035V103039.
[e]Golden Apple Baby Food, Blédina, Villefranche-sur-Saone, France, lot LNHZHP.
[f]Plain yogurt, Danone, Paris, France.
[g]Nutella, Ferrero France, Mont-Saint-Aignan, France, lot 1451B.
[h]HPLC-grade methanol, reference no. 525102, Carlo Erba, Rodano, Italy.
[i]Variomag Multipoint HP15, H+P Labortechnik, Oberschleissheim, Germany.
[j]Bransonic 8200-E3, Branson Ultrasonics, Soest, Netherlands.
[k]Alliance 2690 separations module and ultraviolet light detector model 2487, Waters Corp., Milford, MA.
[l]HPLC-grade acetonitrile, reference no. RH1016, Rathburn, Walkerburn, UK.
[m]Milli-Q Academic System, Millipore Corp., Billerica, MA.
[n]Rotating paddle, AT 7, Sotax, Allschwil, Switzerland.
[o]Alliance 2690 separations module, Waters.
[p]Brownlee Spheri-5 RP-8 column, 5-μm particle size, 100 × 4.6 mm (for assay) or 220 × 4.6 mm (for degradation products), PerkinElmer Inc., Norwalk, CT.
[q]Ultraviolet light detector model 2487, Waters.
[r]Chromatography server, LabSystems, Altrincham, UK.
[s]XChrom version 2.10, LabSystems.
[t]Nucleosil 100-5 C_{18} AB column, 5-μm particle size, 250 × 4 mm, Macherey-Nagel, Düren, Germany.
[u]Novartis Pharma, Basel, Switzerland, lot 2990005001.

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